



Comparison of maternal serum calcidiol and microRNA-1323 expression in term and early preterm births

Term ve erken preterm doğumlarda maternal serum kalsidiol ve mikroRNA-1323 ekspresyonunun karşılaştırılması

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Abstract

Objective: Preterm birth remains a leading cause of neonatal morbidity and mortality. Maternal vitamin D status and epigenetic regulation may contribute to its pathogenesis. This study aimed to analyze differences in subject characteristics, calcidiol [25(OH)D] levels, and maternal blood microRNA-1323 (miRNA-1323) expression between term and early preterm (28-34 weeks) deliveries.

Materials and Methods: An analytical observational study with a comparative cross-sectional design was conducted among 80 parturient women, including 40 term (37-42 weeks) and 40 early preterm deliveries. Calcidiol levels were measured using enzyme-linked immunosorbent assay, and miRNA-1323 expression was analyzed by quantitative reverse transcription polymerase chain reaction with the ΔCq method. Statistical analyses included normality, non-parametric, and correlation tests ($p < 0.05$).

Results: Mean maternal calcidiol levels were significantly higher in the early preterm group than in the term group (27.49 ± 9.18 vs. 23.34 ± 9.64 ng/mL; $p = 0.022$), although both remained below the normal range. Median miRNA-1323 expression was also higher in the early preterm group, but not statistically significant ($p = 0.709$). No significant correlation was observed between maternal calcidiol levels and miRNA-1323 expression in either group, indicating that these biomarkers were not directly associated in the present study and supporting further investigation into their individual contributions to early preterm birth.

Conclusion: Maternal calcidiol levels differed significantly between term and early preterm deliveries, whereas miRNA-1323 showed a non-significant increasing trend. Both biomarkers may reflect biological changes associated with preterm birth.

Keywords: Calcidiol [25(OH)D], miRNA-1323, term delivery, early preterm delivery (28-34 weeks), biomarker, epigenetics

Öz

Amaç: Preterm doğum, yenidoğan morbiditesi ve mortalitesinin önde gelen bir nedeni olmaya devam etmektedir. Maternal D vitamini durumu ve epigenetik düzenleme, bu durumun patogeneğinde rol oynayabilir. Bu çalışma; term ve erken preterm (28-34 hafta) doğumlar arasında olgu özellikleri, kalsidiol [25(OH)D] düzeyleri ve maternal kan mikroRNA-1323 (miRNA-1323) ekspresyonu açısından farklılıkları analiz etmeyi amaçlamıştır.

Gereç ve Yöntemler: Karşılaştırmalı kesitsel tasarıma sahip analitik ve gözlemsel bir çalışma; 40 term (37-42 hafta) ve 40 erken preterm doğum olmak üzere toplam 80 doğum yapan kadın üzerinde yürütülmüştür. Kalsidiol düzeyleri *enzyme-linked immunosorbent assay* yöntemiyle ölçülmüş, miRNA-1323 ekspresyonu ise ΔCq yöntemi kullanılarak reverse transkriptaz polimeraz zincir reaksiyonu ile analiz edilmiştir. İstatistiksel analizler; normallik, parametrik olmayan testler ve korelasyon testlerini kapsamıştır ($p < 0,05$).

PRECIS: Maternal calcidiol levels differed significantly between term and early preterm births, while miRNA-1323 exhibited a non-significant trend, suggesting distinct biological changes.

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Bulgular: Her iki grupta da değerler normal aralığın altında kalmasına rağmen, ortalama maternal kalsidiol düzeyleri erken preterm grubunda term grubuna kıyasla anlamlı derecede yüksek bulunmuştur ($27,49 \pm 9,18$ 'e karşılık $23,34 \pm 9,64$ ng/mL; $p=0,022$). Medyan miRNA-1323 ekspresyonu da erken preterm grubunda daha yüksek saptanmış, ancak bu fark istatistiksel olarak anlamlı bulunmamıştır ($p=0,709$). Her iki grupta da maternal kalsidiol düzeyleri ile miRNA-1323 ekspresyonu arasında anlamlı bir korelasyon gözlenmemiştir; bu durum, söz konusu biyobelirteçlerin bu çalışmada doğrudan ilişkili olmadığını göstermekte ve erken preterm doğuma katkılarına dair daha ileri araştırmaların gerekliliğini desteklemektedir.

Sonuç: Maternal kalsidiol düzeyleri term ve erken preterm doğumlar arasında anlamlı farklılık gösterirken, miRNA-1323 istatistiksel olarak anlamlı olmayan bir artış eğilimi sergilemiştir. Her iki biyobelirteç de preterm doğumla ilişkili biyolojik değişiklikleri yansıtır olabilir.

Anahtar Kelimeler: Kalsidiol [25(OH)D], miRNA-1323, term doğum, erken preterm doğum (28-34 hafta), biyobelirteç, epigenetik

Introduction

Term pregnancy (39-41 weeks) is associated with optimal neonatal outcomes, whereas preterm birth (<37 weeks) remains a major contributor to perinatal morbidity and mortality worldwide⁽¹⁻³⁾. In Indonesia, preterm birth affects approximately 10-15% of live births and is a leading cause of adverse neonatal outcomes and long-term disabilities^(4,5).

The relationship between maternal vitamin D status and preterm birth remains controversial. While several studies have linked vitamin D deficiency to adverse pregnancy outcomes, including prematurity, others have reported inconsistent findings⁽⁶⁻¹⁰⁾. Vitamin D exerts immunomodulatory and gene-regulatory effects through the vitamin D receptor (VDR), with microRNAs (miRNAs) increasingly recognized as important mediators of these pathways⁽¹¹⁻¹³⁾.

Extensive research has sought to enhance the predictability of preterm birth using maternal blood biochemical markers, some of which demonstrate high predictive validity⁽¹⁴⁻¹⁸⁾. In this context, microRNA-1323 (miR-1323) is a compelling candidate because of its role in the regulation of placental trophoblasts and its hypothesized function as an epigenetic mediator linking maternal vitamin D status to placental inflammation⁽¹⁹⁻²³⁾. However, studies investigating the specific relationship between maternal calcidiol [25(OH)D] levels and miR-1323 expression in term and early preterm (28-34 weeks) deliveries remain scarce and heterogeneous, highlighting a critical knowledge gap. Therefore, this study aimed to evaluate differences in maternal calcidiol levels and miRNA-1323 expression between these groups.

Materials and Methods

Study Design and Setting

This study employed an analytical, observational framework with a comparative cross-sectional design to investigate biomarkers associated with gestational outcomes. The clinical phase, including screening and sample collection, was conducted within the Obstetric Emergency Units (PONEK) at Dr. M. Djamil Central General Hospital and Hermina Hospital in Padang, West Sumatra, Indonesia. Laboratory and molecular processing—encompassing serum isolation, enzyme-linked immunosorbent assay (ELISA), and quantitative reverse transcription polymerase chain reaction (RT-qPCR)—were performed at the Biomedical Laboratory, Faculty of Medicine,

Andalas University. Participants were recruited between February and November 2025.

Participant Recruitment and Selection Criteria

Based on an a priori calculation [$\alpha=0.05$, power=90%, pooled SD=2.66⁽²⁴⁾, minimum difference=1], a minimum of 17 participants per group was required. To ensure robust power for the miRNA-1323 analysis, 40 participants per group were enrolled. A total of 80 parturient women were enrolled and equally distributed into two distinct clinical groups based on their gestational age at presentation: the term delivery group (≥ 37 to 42 weeks of gestation; $n=40$) and the early preterm delivery group (28 to 34 weeks of gestation; $n=40$). Gestational age was determined from the date of last menstrual period and confirmed by crown-rump length measurement on first-trimester ultrasonography. In the early preterm group, active uterine contractions and labor status were continuously documented by cardiotocography.

The inclusion criteria required participants to be healthy, pregnant women with singleton pregnancies who voluntarily provided written informed consent prior to enrollment. Participants were excluded if they presented with maternal overweight/obesity (body mass index ≥ 25.0 kg/m²), maternal anemia (hemoglobin <10.5 g/dL), or clinical/laboratory evidence of infection, defined as a white blood cell count exceeding 15,000/ μ L at presentation. Maternal overweight and obesity were controlled for as potential confounders because excess adiposity is associated with vitamin D deficiency and altered VDR-PPAR γ signaling, which may modify the biological activity of 1,25(OH)₂D₃ and, consequently, influence downstream placental gene regulation, including miRNA expression^(24,25). Furthermore, women with chronic systemic conditions (severe chronic diseases, preexisting or gestational diabetes mellitus, chronic hypertension, cardiovascular anomalies, or renal insufficiency), major gestational complications (preeclampsia with blood pressure $\geq 160/100$ mmHg), known fetal structural or chromosomal abnormalities, a history of long-term immunosuppressive or chronic drug therapies, or blood-borne infectious diseases (hepatitis B/C, human immunodeficiency virus, or syphilis) were strictly excluded from the study.

Blood Sample Collection and Serum Processing

During the latent phase of labor, a 5 mL peripheral venous blood sample was collected from each participant. Serum was isolated by centrifugation and stored at -80 °C until molecular analysis.

Quantification of Maternal Serum Calcidiol Levels

Maternal serum calcidiol [25(OH)D] concentration, serving as the definitive circulating indicator of maternal vitamin D status, was quantitatively determined using a commercial solid-phase ELISA kit in accordance with the manufacturer’s strict experimental guidelines. Absorbance was read at 450 nm using a microplate reader. Sample concentrations were calculated by interpolation from a standard linear curve generated simultaneously with the assays, with values expressed in nanograms per milliliter (ng/mL).

Molecular Quantification of Blood miRNA-1323 Expression

Total RNA was extracted from maternal blood using standardized, column-based purification protocols optimized for small RNA preservation. The purity and concentration of the isolated RNA were spectrophotometrically evaluated. Total RNA was subsequently reverse-transcribed into complementary DNA (cDNA) using specific stem-loop primers targeting microRNA. MicroRNA reverse transcription was carried out using a specialized cDNA synthesis kit. Total RNA was extracted from maternal blood samples using a standardized protocol optimized for small RNA preservation. Following reverse transcription to cDNA, the expression of miRNA-1323 was quantified using real-time qPCR. Small nuclear RNA U6 was used as the endogenous reference gene for normalization. Relative expression levels were calculated using the comparative 2^{-ΔΔCt} method and expressed as fold changes relative to the control group.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and approved by the Health Research Ethics Committee of the Faculty of Medicine, Andalas University (approval no: 642/UN.16.2/KEP-FK/2024, date: 23.12.2024). Institutional permission was obtained from Dr. M. Djamil

Central General Hospital and Hermina Hospital Padang (no: 1581/HRD/RSHPAD/V/2025). Written informed consent was obtained from all participants prior to enrollment.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov test. Continuous variables were compared using the independent t-test or the Mann-Whitney U test, while categorical variables were analyzed using the chi-square test or Fisher’s exact test. Correlations between maternal calcidiol levels and miRNA-1323 expression were evaluated using Pearson’s or Spearman’s correlation test, as appropriate. A p-value <0.05 was considered statistically significant.

Results

Eighty participants were enrolled, including 40 term deliveries and 40 early preterm deliveries. Baseline characteristics were comparable between groups (Table 1). Statistical analysis revealed that baseline parameters did not differ significantly. Quantitative analysis of maternal circulating calcidiol [25(OH)D] demonstrated distinct profiles in the two experimental groups (Table 2). Maternal calcidiol levels were significantly higher in the early preterm group than in the term group, although both groups remained within the insufficient range (<30 ng/mL), which consistently indicates widespread gestational vitamin D insufficiency in the study population. As detailed in Table 3, maternal miRNA-1323 expression was higher in the early preterm group than in the term group, but the difference was not statistically significant. To determine whether a direct endocrine-epigenetic axis regulates the timing of labor, we performed a correlation analysis between maternal serum calcidiol concentrations and

Table 1. Baseline characteristics of the study participants in term and early preterm (28-34 weeks) deliveries

Characteristic	Classifications			
	Term delivery (n=40)		Early preterm delivery (n=40)	
	f	%	f	%
Maternal age (years)				
18-34 years	35	87.5	36	90
High risk	5	12.5	4	10
Hemoglobin (g/dL)				
Anemic (<10.5 g/dL)	0	0	0	0
Non-anemic	40	100	40	100
Leukocyte (/μL)				
Normal (<15.000/uL)	40	100	38	95
Abnormal	0	0	2	5
Parity				
Primipara	14	35	14	35
Multipara	26	65	26	65

the relative expression ratios of blood miRNA-1323 (Table 4). No significant correlation was found between maternal calcidiol levels and miRNA-1323 expression in either group, as illustrated by the scatter plots and fitted regression lines in Figure 1.

Discussions

The absence of significant differences in baseline socio-demographic and hematological characteristics suggests that early preterm birth in this study population may not be primarily explained by traditional risk factors. This finding departs from classical risk frameworks that link maternal age and anemia to prematurity and instead supports the concept of preterm birth as a multifactorial syndrome driven by multiple biological pathways that extend beyond routine clinical parameters⁽²⁶⁻²⁸⁾. The association between maternal vitamin D status and preterm birth remains inconsistent across the literature. Several studies have reported that low maternal vitamin D levels increase the risk of preterm delivery, whereas others have found no significant relationship after adjustment for confounding factors^(6,8-10). These discrepancies may be attributed to differences in study populations, gestational age at blood sampling, geographic sunlight exposure, and definitions of vitamin D deficiency. Although reduced calcidiol availability has been implicated in the inflammatory pathways leading to preterm birth, the significantly higher maternal calcidiol levels observed in the early preterm group suggest that circulating calcidiol concentrations alone may not adequately represent vitamin D biological activity or its downstream molecular effects^(29,30). This finding underscores the need to consider additional regulatory mechanisms, including placental molecular pathways, in interpreting the role of vitamin D in early preterm birth.

Nevertheless, vitamin D insufficiency should be considered one component of the multifactorial mechanisms underlying early preterm birth. Maternal and fetal stress responses, placental dysfunction, oxidative stress, and inflammatory activation may interact synergistically to accelerate parturition⁽³⁰⁻³⁵⁾. In addition, alterations in microRNA expression, as observed in this study, may further modulate immune and inflammatory pathways involved in preterm labor⁽¹³⁾. Collectively, these findings suggest that maternal vitamin D insufficiency contributes to the biological milieu associated with early preterm delivery, acting alongside multiple interconnected pathways that promote premature activation of labor.

The findings on maternal microRNA expression in preterm birth remain inconsistent across studies. Some studies reported no significant differences in miRNA profiles between preterm and term deliveries, while others demonstrated altered circulating miRNA expression associated with preterm birth risk⁽¹⁹⁻²³⁾. These discrepancies may reflect differences in the specific miRNAs studied, gestational timing of sampling, population characteristics, and laboratory methodologies. In this study, the increased expression of miRNA-1323 in early preterm deliveries supports the concept that epigenetic dysregulation is involved in the pathophysiology of prematurity.

Maternal calcidiol levels were significantly higher in the early preterm group than in the term group; however, both groups remained within the vitamin D insufficiency range. The lower calcidiol levels observed at term may reflect physiological depletion in late gestation related to prolonged fetoplacental demand, fetal mineralization, hemodilution, and the utilization of maternal vitamin D stores. Therefore, this finding does not

Table 2. Differences in maternal blood calcidiol [25(OH)D] levels between term and early preterm (28-34 weeks) deliveries

Variable	Classifications		p-value
	Term delivery (n=40)	Early preterm delivery (28-34 weeks) (n=40)	
	Mean ± SD	Mean ± SD	
Calcidiol levels [D 25(OH)D] (ng/mL)	23.34±9.64	27.49±9.18	0.022*

*Independent t-test, SD: Standard deviation

Table 3. Differences in maternal blood microRNA-1323 (miRNA-1323) expression in term and early preterm (28-34 weeks) deliveries

Variable	Classifications		p-value
	Term delivery (n=40)	Early preterm delivery (28-34 weeks) (n=40)	
	Median (min-max)	Median (min-max)	
miRNA-1323 ΔCq expression	1.56 (0.04-101.55)	7.79 (0.006-114.35)	0.709**

**Mann-Whitney U

Table 4. Correlation of maternal blood calcidiol [25(OH)D] levels and microRNA-1323 (miRNA-1323) expression between term and early preterm (28-34 weeks) deliveries

Variable	Classifications					
	Term delivery			Early preterm delivery		
	N	r	p-value	N	r	p-value
Vitamin D - miRNA	40	0.26	0.105	40	-0.012	0.943

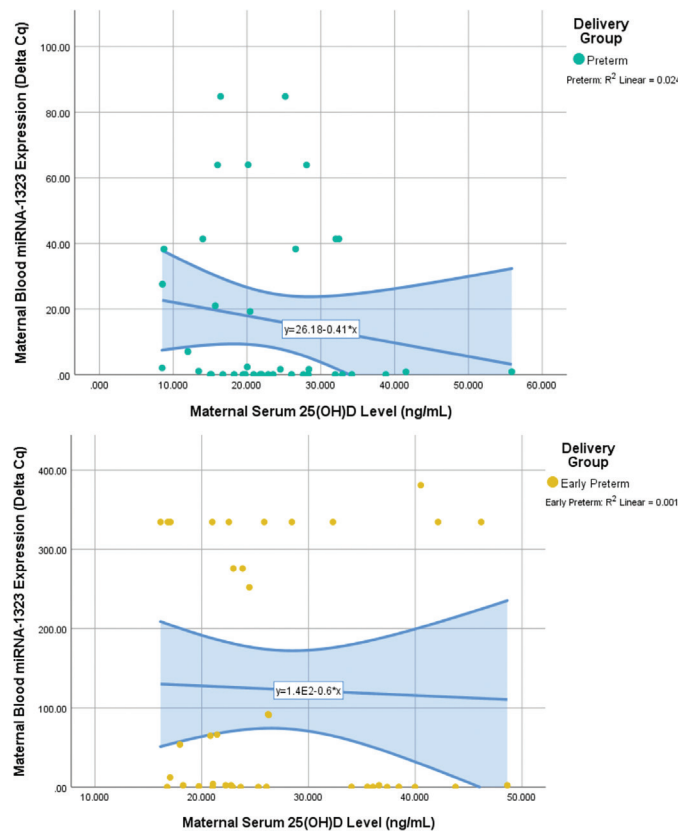


Figure 1. Scatter plot of calcidiol and miRNA-1323 levels in term and early preterm deliveries

miRNA: MicroRNA

contradict the role of vitamin D in pregnancy outcomes but rather highlights the complex and multifactorial regulation of vitamin D metabolism.

Maternal calcidiol and miRNA-1323 represent interconnected but distinct biological pathways involved in pregnancy regulation. Calcidiol reflects maternal immunometabolic and inflammatory status through VDR signaling, whereas miRNA-1323 functions as an epigenetic regulator associated with placental stress and trophoblast activity. Despite their theoretical relationship, no significant correlation was observed between maternal calcidiol levels and miRNA-1323 expression in either term or early preterm deliveries. Furthermore, calcidiol levels remained insufficient in both groups, whereas miRNA-1323 expression tended to be higher in early preterm deliveries, suggesting that both biomarkers are involved in related biological processes that eventually lead to preterm deliveries.

These findings are consistent with previous studies reporting inconsistent associations between maternal vitamin D status, miRNA expression, and prematurity^(9,10,22). Such variability may result from differences in study populations, gestational age at sampling, vitamin D deficiency criteria, environmental factors, and the specific miRNAs analyzed. Nevertheless,

substantial evidence supports the independent relevance of both biomarkers, with low maternal vitamin D levels and altered circulating miRNA profiles each associated with an increased risk of preterm birth^(6,7,19,23).

Collectively, the results suggest that calcidiol and miRNA-1323 contribute to prematurity through complementary, rather than directly linked, mechanisms. While vitamin D status primarily reflects systemic maternal immune-inflammatory regulation, miRNA-1323 may represent localized epigenetic and placental stress responses. Therefore, the absence of a direct correlation reinforces the multifactorial nature of early preterm labor, in which nutritional, immunological, and epigenetic pathways interact without necessarily exhibiting a linear relationship.

Study Limitations

Strengths of this study include balanced groups, strict eligibility criteria, and standardized ELISA and RT-qPCR measurements. However, the cross-sectional design limits causal inference; calcidiol was measured only at delivery; maternal smoking history, previous preterm birth, and vitamin D supplementation during pregnancy were not accounted for; and the analysis was restricted to a single miRNA-1323, potentially limiting the comprehensiveness of the epigenetic assessment.

Conclusion

This study found that maternal sociodemographic and clinical characteristics were comparable between term and early preterm deliveries. Although maternal serum calcidiol concentrations differed significantly between groups, vitamin D insufficiency was prevalent in both groups. No significant differences in maternal miRNA-1323 expression were observed, nor was any significant correlation identified between calcidiol levels and miRNA-1323 expression. These findings suggest that calcidiol and miRNA-1323 reflect distinct but complementary biological pathways involved in parturition, representing systemic immunometabolic and localized epigenetic processes, respectively.

Future studies should employ prospective longitudinal designs with larger sample sizes to clarify the temporal relationship between vitamin D status, miRNA expression, and preterm birth. Serial assessment of maternal calcidiol levels throughout pregnancy and broader evaluation of epigenetic markers are also warranted to better understand their potential roles as both predictive and mechanistic biomarkers of preterm labor.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Health Research Ethics Committee of the Faculty of Medicine, Andalas University (approval no: 642/UN.16.2/KEP-FK/2024, date: 23.12.2024). Institutional permission was obtained from Dr. M. Djamil Central General Hospital and Hermina Hospital Padang (no: 1581/HRD/RSHPAD/V/2025).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.A., Concept: D.A., Y., J., M., Design: D.A., Y., J., M., Data Collection or Processing: D.A., Analysis or Interpretation: D.A., Y., J., M., Literature Search: D.A., Writing: D.A., Y., J., M.

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